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Invited review article

Prevention of food allergy – Early dietary interventions☆

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IgE, Immunoglobulin E; WHO, World Health Organization; Th-2, T-helper type 2; FLG, Filaggrin; STAR, Solids Timing for Allergy Research; HEAP, Hen's Egg Allergy Prevention; EAT, Enquiring About Tolerance; BEAT, Beating Egg Allergy Trial; LEAP, Learning Early about Peanut Allergy; PUFAs, polyunsaturated fatty acids; SPT, skin prick test; OFC, oral food challenges; NNT, number needed to treat; ITT, intention-to-treat

ABSTRACT

The prevalence of food allergy has increased over the last 30 years and remains a disease, which significantly impacts on the quality of life of children and their families. Several hypotheses have been formulated to explain the increasing prevalence; this review will focus on the hypothesis that dietary factors may influence the development of food allergy. Historically, the prevention of food allergy has focused on allergen avoidance. However, recent findings from interventional studies have prompted a shift in the mind set from avoidance to early introduction of potentially allergenic foods. This review aims to facilitate a better understanding of contemporary research studies that make use of early introduction of common allergenic foods into infant diets as a preventative strategy against the development of food allergy.

Background

The prevalence of food allergy has been on the rise over the last 30 years with 6–8% of children being affected worldwide; the disease burden is higher for infants and preschool children.[2–4] Food allergy is primarily classified as immunoglobulin E (IgE)-mediated food allergy, non-IgE mediated food allergy or mixed IgE and non-IgE mediated food allergy.[5] IgE-mediated food allergies are type 1 immediate hypersensitivity reactions with a quick onset of symptoms usually within a few hours of exposure to a food antigen compared to non-IgE mediated food allergy where there is a delayed onset of symptoms following exposure to a food.[2] There is strong evidence showing the significant impact food allergies can have on the quality of life of the children affected and their families including emotional, psychological and financial burdens.[6–8] There is as yet no cure for IgE-mediated food allergy and the main treatment remains avoidance; thus, understanding the cause and developing strategies for the prevention of allergy has been at the forefront of current allergy research.

History of food allergy

In the 1960s, most infants were exposed to solids (complementary feeding) by 4 months of age[9]; however, in the 1970s new guidelines were introduced recommending a delay in the introduction of solids until after 4 months due to an assumption that early introduction of gluten was contributing to a rise in coeliac

☆ This review is a modified and updated version of a similar invited review that appeared in the Journal of Allergy and Clinical Immunology in April 2016.[1]

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disease which was observed at the time.[10] The World Health Organisation (WHO) recommended a further delay in the introduction of solid food in the 1990s to 6 months of age, and advised parents to delay the introduction of allergenic solids such as egg and peanut to 10 months and 3 years, respectively.[9] More specifically, in 1998 the UK Department of Health suggested that atopic pregnant and lactating women as well as children in the first 3 years of life should avoid the consumption of peanuts.[11,12] Despite these recommendations being intended for 'at risk' families they were more widely adopted.[13,14] A WHO systematic global review in 2002, which looked at exclusive breastfeeding for 6 months, reported no benefits of introducing complementary foods between 4 and 6 months of age for allergy prevention; despite this, recommendations for exclusive breastfeeding of infants in both developed and developing countries for the first six months of age were made.[15] A similar stance was adopted in the United States with a consensus document recommending that the optimal age for selected foods should be 6 months, specifically dairy products at 12 months, hen's egg at 24 months and at the earliest, peanut, tree nuts, fish and seafood at 36 months of age.[16]

Over the last few decades, despite these measures initiated to prevent allergy by delaying the introduction of allergenic foods, the prevalence of food allergy has continued to rise even in countries where dietary avoidance is practiced. Factors such as genetic variation, ethnicity, gender, hygiene, maternal diet in pregnancy and breastfeeding may all be contributing to the rising prevalence of allergy. Several hypotheses as to the cause for the rising prevalence of food allergies have been postulated and have been important in driving current research aimed at the prevention of food allergy. These hypotheses include the hygiene hypothesis, the vitamin D hypothesis and the dual-barrier hypothesis.

Hygiene hypothesis

The hygiene hypothesis describes the protective influence early-life microbial exposure has on the development of allergic diseases.[17] Strachen first proposed that having older siblings had a protective effect on the development of hay fever in younger siblings, possibly due to exposure to common childhood infections, but also maternal contact with older children in the prenatal period.[18] Since then, several studies have shown that various factors that increase exposure to pathogens, microbes and infections after birth can influence the host microbiome and immune defence system which plays a key role in the development of immune regulation as well as the development of oral tolerance.[19,20] Factors such as the mode of delivery, communal childcare, pets at home and birth order, which can influence exposure to micro-organisms, have been shown to influence the development of allergic disease.[19,21,22] The recent advances in our understanding of the role of the microbiome and gastrointestinal barrier function has led to a plethora of research in this area in relation to their role in food allergy.[23,24]

Vitamin D hypothesis

A more recent hypothesis has been that low vitamin D levels increase the risk of developing food allergy. Coincidentally, the rise in food allergy has occurred in conjunction with the increasing prevalence of vitamin D deficiency which has led to increased research into understanding the link between the two conditions.[25] In the HealthNuts population-based cohort study in Australia, vitamin D insufficiency was found to be associated with challenge-proven food allergy at 12 months of age.[26] More in-depth research into the genetic polymorphisms affecting vitamin D metabolism in this cohort has shown that altering the bioavailability of serum $25(OH)D_3$ could have a role in the development of food allergy.[27]

Dual-barrier hypothesis

The dual-barrier hypothesis has also played a key role in trying to explain the increasing prevalence of allergy. The most obvious and dominant route of food allergen exposure is through consumption, but allergen exposure may also occur through the skin and possibly the respiratory tract if inhaled. Atopic children experience a T-helper type 2 (Th-2) allergen specific immune response that occurs on exposure to a food allergen which results in the production of IgE antibodies for that specific allergen.[28] Non-atopic children absorb these foreign antigens without causing an immune host response, which allows for the development of oral tolerance.[28] The dual-barrier hypothesis suggests that early allergic sensitization to foods and environmental allergens occurs through a damaged or weakened skin barrier (i.e. eczema, filaggrin (FLG) loss-of-function mutations)[19,29]; thus there is a close relationship that exists between food allergy and eczema. A recent study showed that approximately 50% of children with eczema developed food allergy by 1 year of age.[30] Strid *et al.* had previously demonstrated that epicutaneous exposure to peanut protein in mice prevented the normal induction of oral tolerance but also enhanced Th2 responses including increasing IgE levels on gastrointestinal exposure.[31] This was further supported by Lack *et al.'s* paper which showed that use of topical peanut-oil based emollient preparations on children, which exposed them to peanut allergen through inflamed skin, was associated with peanut allergy.[32] Horimukai *et al.* also found that having eczematous skin increased allergic sensitization to egg white in the first 8 months of life.[30] Understanding the involvement of the skin barrier in food allergy has included further research into the role of FLG, which is known to play a vital role in epithelial barrier function and development of eczema. Brough *et al.* looked at the effect of environmental peanut exposure in a population-based birth cohort and found that children who carried a FLG mutation had an increased risk of peanut sensitization and allergy associated with early life environmental peanut exposure.[33] This is further supported by research from the Isle of Wight cohort for which there was a significant total effect noted of FLG mutations on the risk of food allergy later in childhood (10 years) but also an indirect effect between eczema and food allergy sensitization in early childhood.[34] Interestingly, recent work by Kelleher *et al.* demonstrate that a permeable skin barrier on day two of life is associated with food sensitization and allergy at 2 years of age, even in the absence of eczema.[29] Studies into improving the skin barrier in order to decrease the risk of food allergy in children are underway; indeed, in a pilot study Simpson *et al.* demonstrated in a cohort of neonates that daily emollient applied from birth resulted in a 50% relative risk reduction in the development of eczema at 6 months of age.[35]

The role of diet in food allergy

With the continual rise in prevalence of food allergy despite advisory measures of avoidance, the last 10 years have witnessed an increasing body of evidence based on epidemiological studies that challenge the idea of dietary avoidance for the prevention of food allergy.[36] This has led to research looking into the alternate strategy of early introduction of foods for the prevention of food allergy.

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Maternal diet in pregnancy and lactation

The timing of when the sensitization to food or inhalant allergens occurs (i.e. in utero or in the post-natal period) has been considerably debated. There is little data available that supports the manipulation of the maternal diet during pregnancy or lactation to prevent food allergy. Kramer and Kakuma conducted a Cochrane Systematic Review which included evidence from five trials, and overall concluded that advising an antigen avoidance diet to women during pregnancy and lactation was unlikely to reduce the risk of giving birth to an atopic child.[37] Similarly, there have been studies that have shown no reduction in risk of cow's milk and egg allergy in infants of mothers who were avoiding cow's milk and egg in pregnancy.[38] Lack *et al.'s* cohort study using data from the Avon Longitudinal Study of Parents and Children found no association between the development of peanut allergy and maternal consumption of peanuts during pregnancy, but also found no detectable specific IgE to peanuts in cord blood samples obtained.[32] Similarly, Fox *et al.* found that maternal peanut consumption during pregnancy and lactation had no effect on peanut sensitization in infancy.[12] However, Sicherer *et* al found that in their atopic cohort of infants aged 3–15 months (CoFAR Study), maternal ingestion of peanut during pregnancy was strongly associated with high peanut sensitization.[39]

Breastfeeding

Breastfeeding has long been considered the infant feed of choice; despite this widely accepted knowledge exclusive breastfeeding rates and duration of breastfeeding remains sub-optimal in most countries. For example, according to WHO, the highest rates of exclusive breastfeeding for the first 6 months of life occur in the Eastern Mediterranean region of the world (40% of infants) compared to only 29% of infants in the Western Pacific region of the world.[40] Nonetheless, breastfeeding has been considered to be a factor that could influence food allergy development through several mechanisms. These include potentially anti-allergic immune properties in the milk, the possibility that prolonged breastfeeding may delay allergen introduction, but also the presence of antibodies within breast milk that may combine with food antigens to induce tolerance.[1] However, there is limited evidence on the direct impact breastfeeding has on the development of food allergy. The majority of studies so far show no benefit of breastfeeding over cow's milk formulae on the development of allergy to foods such as cow's milk, soya, and egg.[38] Lack *et al.'s* study investigating factors influencing food allergy found that the duration of breastfeeding was not significantly associated with peanut allergy and mothers of the children who had peanut allergy had not consumed more peanuts during breastfeeding compared to the mothers of the children without peanut allergy.[32]

Timing of infant food introduction

The timing of food introduction and oral tolerance has been at the forefront of paediatric food allergy research over the last decade. The concept of oral tolerance is well understood in murine models of which previous work has shown how early and regular oral exposure induces clinical tolerance and immunological change to food allergens.[41,42] Further research in humans has also shown that early exposure to food allergens can lead to oral tolerance,[43] which we will discuss in greater detail below.

Cow's milk allergy

Cow's milk is the most common source of infant food allergy, affecting 1.4–3.8% of young children.[44] It can be IgE-mediated with immediate reactions such as urticaria, angioedema and/or anaphylaxis or non-IgE mediated which often manifests with skin or gastrointestinal symptoms.[45,46] A large observational cohort study looked at the relationship between the age of introduction of cow's milk and cow's milk sensitization at 2 years of age. A delay in the introduction of cow's milk products was associated with an increased risk of developing atopy at 2 years old, especially eczema.[47] A prospective study which aimed to determine risk factors for developing cow's milk allergy found that infants started on cow's milk protein formula within the first 14 days of life had lower rates of IgE-mediated cow's milk allergy compared to those where cow's milk formula was introduced between 105 and 194 days of life, 0.05% versus 1.75%, respectively ($p < 0.001$).[48] In keeping with this data, Boyle *et al.'s* recent study confirmed that avoidance of cow's milk (i.e. using an extensively hydrolysed whey formula) for the prevention of developing atopy at 12 months, more specifically eczema, in high-risk infants was not protective.[49]

Egg allergy

Egg allergy is the second most common food allergy with a prevalence rate of approximately 2.5%.[45,50] Several studies have looked at the introduction of egg in various forms (i.e. baked, cooked). The Solids Timing for Allergy Research (STAR) trial looked at infants with moderate to severe eczema of which the intervention group had egg (pasteurized raw whole egg powder) introduced from 4 months of age compared to the control group who avoided egg (rice powder).[42] Although the results were not statistically significant, a lower proportion of infants in the intervention group were diagnosed with IgE-mediated egg allergy compared to the control group, 33–51%, respectively (relative risk 0.65, CI 0.38–1.11, $p = 0.11$).[42] Nwaru *et al.* found that in their cohort of 994 Finnish children, having their first introduction of eggs occur when they were 10.5 months or older was associated with sensitization to food allergens at 5 years of age.[51] Data from the Australian HealthNuts cohort also showed that delayed introduction of egg until 10–12 months or >12 months old was associated with a significantly increased risk of egg allergy compared to those infants who had early introduction at 4–6 months of age.[52] Furthermore, in the early introduction group, first exposure to cooked egg reduced the risk of egg allergy compared to first exposure of egg in baked goods (OR, 0.2, 95% CI 0.06–0.71).[52] Similarly, Leonard *et al.* found that the initiation of baked egg diet accelerated the development of egg tolerance compared to strict avoidance.[53] Not only may the timing of introduction of egg be important, but the form in which egg is introduced may have an impact on the development of tolerance. Further large trials are being conducted including the Hen's Egg Allergy Prevention (HEAP) trial.[54] This study aimed to look at the introduction of egg (pasteurized egg white powder) in the general population with infants receiving egg or placebo three times a week starting at age 4–6 months until 12 months. Provisional results showed that the early consumption of pasteurized hen's egg was not effective in preventing egg allergy at 12 months of age. The majority of the infants who underwent double-blind placebo-controlled food challenges (94%, 16/17) had a positive challenge and in fact, two of the children in the intervention group reacted to the pasteurized egg white powder on first exposure at home (including one that had anaphylaxis).

More recently, the Enquiring About Tolerance (EAT) study,[55,56] which is a randomized controlled trial looking at the early introduction of six common food allergens at 3 months of age (early

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introduction group) alongside breastfeeding compared to exclusively breast-fed infants (standard introduction group), found that the prevalence of egg allergy was significantly lower in the early-introduction group (2.4% vs. 7.3%, $p = 0.01$) in the per-protocol analysis. Egg allergy occurred in 3.7% of the early introduction group compared to 5.4% in the standard introduction group (relative reduction 31%, $p = 0.17$). In the EAT Study, egg was eaten as whole hard-boiled egg and the per protocol uptake for egg ingestion was lower compared to the ingestion of the other EAT foods, i.e. peanut and milk, but higher than for sesame, fish, and wheat (which was the last food to be introduced on the study). The low uptake of egg may be related to texture, smell or the logistic demands of boiling and preparing an egg into a feed appropriate for infants. Additional trials are underway such as the Beating Egg Allergy Trial (BEAT)[57] and the Egg Allergy Prevention Trial,[58] which should provide us with greater insight into the safety and efficacy of early egg introduction.

Peanut allergy

Although the prevalence of peanut allergy is less common than milk or egg allergy, it can induce life-threatening anaphylaxis and has been on the rise.[45] The early ecological study by Du Toit *et al.*[59] raised the question whether early peanut introduction may be an ideal strategy for the prevention of peanut allergy. The study looked at infants with peanut allergy in Israel compared to those in the UK and found the prevalence of peanut allergy in the UK to be significantly higher in the UK compared to Israel (1.85% versus 0.17%, $p < 0.001$). Further analysis revealed that peanut was introduced earlier and eaten more frequently and in larger quantities in Israeli infants compared to UK children. Israeli infants between ages 8–14 months were consuming about 7.1 g of peanut protein per month compared to 0 g of peanut protein in children in the UK ($p < 0.001$). The 10-fold increased prevalence of peanut allergy in UK children even after differences in atopy, genetics, social class and peanut allergenicity were accounted for, brought forth the question of whether early peanut introduction and regular consumption may be contributing to the development of peanut allergy. These findings led to the design of the Learning Early about Peanut Allergy (LEAP) study.[60,61] The LEAP study was a randomized controlled study that aimed to assess oral tolerance induction of peanut in high-risk children aged between 4 and 11 months of age in the UK. Infants were randomized to consuming peanut products at least 3 times a week (average of 6 g of peanut protein a week) or completely avoiding any peanut products until 60 months of age. The results from the study demonstrated that in this cohort of high-risk atopic children, early introduction and regular ongoing consumption of peanut resulted in a significant reduction (81% relative reduction, intention to treat analysis) in the number of children with peanut allergy at 60 months of age compared to those who avoided peanut. The intention-to-treat analysis showed that in the peanut avoidance group, 17.2% of the children had challenge-proven peanut allergy at 60 months of age compared to 3.2% in the peanut consumption group. From a safety perspective, 7 of the 319 children randomized to the peanut consumption group reacted to peanut at their baseline oral food challenge (OFC). However, the reactions were not severe enough to require adrenaline and choking on peanut foods was not reported. Many of the participants were breastfeeding at the beginning of LEAP but this was not affected by the early-life introduction of peanut. There were no differences in height, weight or body mass index—a measure of body fat—between the peanut consumers and avoiders.[62] This was true even when the researchers compared the subgroup of children who consumed the greatest amount of peanut protein to those who avoided peanut entirely. In general, the peanut consumers easily achieved the recommended level of 6 g of peanut protein per week, consuming 7.5 g weekly on average. Uptake of peanut consumption was achieved within the first month with participants tolerant of peanut eating increasing amounts of peanut with age and peanut in different foods. LEAP consumers made favourable food choices compared to avoiders. For example, consumers ate fewer chips and savoury snacks. Both groups had similar total energy intakes from food and comparable protein intakes. Peanut consumers enjoyed higher fat intakes as compared to avoiders (the benefits of which are currently being debated in the nutritional literature) and avoiders had higher carbohydrate intake.[62] LEAP participants randomized to peanut consumption had a higher intake of omega 6 polyunsaturated fatty acids (PUFAs), as peanut is rich in PUFAs. Compared to the avoiders at all study time points, the higher ratios of omega 6 to omega 3 intake were not associated with differences in the prevalence of protocol-defined seasonal allergic rhino-conjunctivitis, perennial allergic rhino-conjunctivitis, eczema or asthma. Together, these findings demonstrate the acceptability and safety of this intervention. The LEAP study was able to demonstrate both primary and secondary prevention of the development of peanut allergy by early introduction, i.e. both participants who were sensitized to peanut and those who were not sensitized to peanut at baseline (based on skin prick test (SPT) and specific-IgE levels) had reduced peanut allergy at 60 months if peanut was introduced early. The reduction in peanut allergy translates to a number needed to treat (NNT) of 8.5 for participants with a negative SPT response to peanut (no measurable wheal) and NNT of 4.0 for the participants who had a baseline low-positive peanut SPT response (wheal of 1–4 mm).

The LEAP-On study[63] was an extension study to LEAP, which investigated whether children who consumed peanut remained protected against developing peanut allergy even after cessation of peanut consumption for a period of 12 months. A total of 556 participants (88.5% (556/628)) from the primary trial were enrolled in the follow-on study and the rate of adherence to avoidance was high (90.4% in the peanut-avoidance group, 69.3% in the peanut-consumption group). At 72 months, peanut allergy remained significantly higher in the peanut-avoidance group compared to the peanut-consumption group, 18.6% vs 4.8% ($p < 0.001$), respectively. These clinical findings were associated with immunological changes (levels of Ara h 2 specific peanut IgE, peanut specific IgE and IgG4 levels) suggestive of immune tolerance. For example, participants with peanut allergy at 72 months had higher levels of Ara h 2 specific IgE compared to those who did not have peanut allergy and the mean level of Ara h 2 specific IgE which had declined significantly in the peanut consumption group in the primary trial ($p < 0.001$) remained low at 72 months, after 12 months of peanut avoidance. Contrastingly, the mean levels of Ara h 2 specific IgE in the peanut avoidance group were significantly higher at 60 months and 72 months compared to the peanut consumption group ($p < 0.001$). As for IgG4 levels and the ratio of peanut specific IgG4:IgE, they were both significantly higher in the peanut consumption group compared to the peanut avoidance group ($p < 0.001$) at 60 months, but also at 72 months after a yearlong period of avoidance ($p < 0.001$). However, in the consumption group, values of peanut IgG4 had started to decrease, even at 30 months of age (when peanut consumption was ongoing). LEAP-On demonstrates that for the peanut consumption group, their non-allergic status remained stable over 12 months of avoidance. Therefore, the key finding of the LEAP studies is that early introduction and consumption of peanut until 60 months of age causes a reduction in peanut allergy that persists at 72 months of age, even with a 12-month period of avoidance. Follow-on studies of this cohort are planned to determine if the effects of early tolerance continue to persist for longer.

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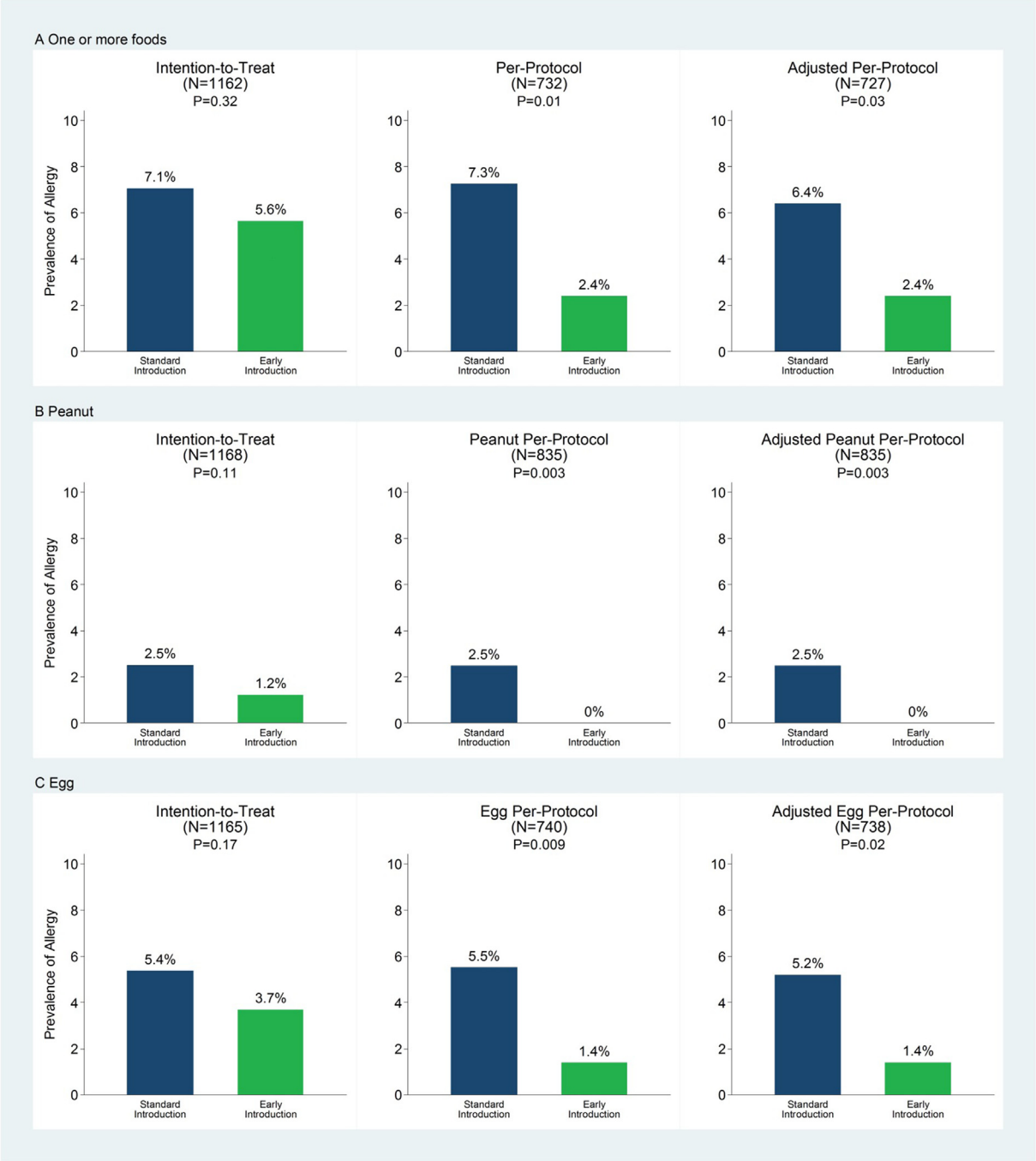

Fig. 1. EAT Study Primary Outcome – Food Allergy. The prevalence of IgE mediated food allergy is shown to one or more of the six intervention foods (Panel **A**), to peanut (Panel **B**) and to egg (Panel **C**). The first column shows the intention-to-treat analysis, the second column the per-protocol analysis and the third column an adjusted per-protocol analysis. The latter was a conservative per-protocol analysis that adjusted the standard introduction group food allergy prevalence by subtracting the number of baseline early introduction group participants who were challenge positive at enrolment and completed the study with a confirmed food allergy from both the numerator (the number of allergic standard introduction group participants) and the denominator (the number of standard introduction group per-protocol adherent participants). *p* Values are based on chi-square analyses (or Fisher's exact test where appropriate).
From Perkin M, Logan K, Tseng A, Raji B, Ayis S, Peacock J *et al.* Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016; 374: 1733–43. Reprinted with permission.

Other food allergens

Early introduction of other food allergens has been studied in cross-sectional studies that use surrogate markers (other than OFC) for the diagnosis of food allergy. For example, Kull *et al.* found that regular consumption of fish in the first year of life was associated with a reduced risk of allergic disease (OR, 0.76; 95% CI 0.61–0.94) and sensitization to food and aeroallergens (OR, 0.76; 95% CI 0.58–1.0) at 4 years of age.[64] However, the diagnosis of fish allergy was based on positive specific IgE level of ≥0.35 kUA/l rather than double-blinded OFCs, which are the gold standard for diagnosis of food allergy.[65] Also, the prevalence of fish

sensitization is not as common as foods such as egg, milk and peanut[66,67] thus making it more challenging to extrapolate this data to other foods allergens. Similarly, a study looking at introduction of wheat found that children exposed to cereals (wheat, barley, rye, oats) after 6 months of age had an increased risk of developing wheat allergy compared to those children where it was introduced before 6 months.[68] Upcoming research work such as the ProNut study,[69] which aims to evaluate the cross-reactivity in nut allergic children through OFCs, may provide us with greater insight into tree nut allergens.

The EAT study[56] also provides important insight into oral tolerance for multiple allergenic foods in a general UK paediatric population. Over 1000 infants were recruited with the initial criteria prior to randomization being that infants had to have been exclusively breast-fed from birth until enrolment at 3 months of age. In the study, the intervention group had six potentially allergenic foods (cow's milk, egg, wheat, sesame, fish, peanut) introduced into their diets by 4 months of age compared to the control group which followed standard UK government advice of exclusively breastfeeding until 6 months of age with no introduction of allergenic foods before 6 months. The randomized sequence of food introductions for the early introduction group was cow's milk (yogurt) first, followed by peanut, egg, sesame and whitefish in random order with wheat introduced last. The main outcome was a challenge proven diagnosis of allergy to one or more of the six foods at 1 year and 3 years of age. The intention-to-treat (ITT) analysis showed that 7.1% of the infants in the standard group developed food allergy to one or more of the six interventional foods compared to 5.6% in the intervention group ($p = 0.32$). In the per-protocol analysis, the prevalence of any food allergy was significantly lower in the early-introduction group compared to the standard-introduction group (2.4% vs 7.3%, $p = 0.01$). Furthermore, the prevalence of peanut allergy (0% vs 2.5%, $p = 0.003$) and egg allergy (1.4% vs 5.5%, $p = 0.009$) was less in the early-introduction group compared to the standard-introduction group (Fig. 1).

Favourable cutaneous immunological changes were also noted; in the ITT analysis the risk of having a positive SPT to any food was 22% lower in the early introduction group compared to the standard introduction group at 12 months of age and 36 months of age, $p = 0.07$ and $p = 0.47$, respectively. Although both were not significant, a significant difference was seen in the per-protocol analyses. Both at 12 months and 36 months, the early introduction group had a significantly lower rate of SPT to any food compared to the standard introduction group, 42% ($p = 0.01$) and 67% ($p = 0.002$), respectively.

Adherence

In the EAT study, the rate of adherence in the standard introduction group was high with 92.9% (524/564) of the participants meeting the per protocol criteria. The early introduction group proved to be more challenging with only 42.8% (208/486) of the participants being per protocol compliant. More specifically, in the early introduction group the food that was tolerated least was hen's egg (43.1%). Further analysis included calculation of the weekly mean consumption of egg and peanut protein, which was divided into quartiles between enrolment and 6 months of age. Using this data, predictive probability plots were generated which showed that higher consumption of peanut and egg was associated with lower sensitization and prevalence of allergy to the specific food. Importantly, what was adhered to extremely well was exclusive breastfeeding. Furthermore, for the infants who were in the standard-introduction group, they had to continue exclusive breastfeeding until at least 5 months of age.

In the LEAP study, the overall adherence rate of the two assigned interventions was high (92.0%). This was similarly reflected in the LEAP-On study with an overall adherence to the intervention of peanut avoidance in the follow-up group being 80.0%. There are many possible explanations for the differences in adherence rates between the studies including factors relating to the food/s (e.g. yoghurt is easily served, and a common infant feed), mother and family (education and ethnic differences), and ongoing study support (LEAP offered significantly more study contact than did EAT).

Non-IgE mediated allergy

Most of the focus on early intervention studies has been on IgE-mediated food allergy. However, of increasing interest is the recognition and diagnosis of non-IgE mediated food allergy, which often presents with a delayed onset of symptoms that are usually gastrointestinal or dermatological in nature.[70] The EAT study collected data on parental reporting of non-IgE mediated symptoms such as colic, vomiting, posseting, diarrhoea and constipation. They found that infants in the early intervention group reported significantly more non-IgE type symptoms e.g. eczema flares and colic, than the standard intervention group at 4–6 months of age, 8.6% and 3.8%, respectively ($p < 0.001$). However, rates of non-IgE symptoms at any time point were equivalent between groups suggesting that the introduction of the study foods was associated with the reporting of these symptoms regardless of when they were introduced. Specifically, 11.9% of participants in the early introduction group reported non-IgE type symptoms to one or more of the early introduction foods at any point (4–12 months) compared to 9.6% of the standard introduction group ($p = 0.20$). Further research into understanding whether early intervention studies can impact the development of non-IgE mediated food allergies will be important to better understand all types of childhood allergic disease.

Future research

Over the last few years, based on the findings from LEAP, there has been a change in practice by clinicians and advice given to parents of children at risk of peanut allergy. Consensus statements from various global allergy, paediatric and dermatology societies have been published encouraging the early introduction of peanut to infants at risk of developing food allergy.[71–74] From this, Australasian guidelines have been updated to include the introduction of allergenic solid foods including peanut butter, cooked egg, dairy and wheat products to all children in the first year of life, including those at high risk of allergy.[75]

The exact timing of early dietary interventions remains an important question that will require further research. In the LEAP study, 76 of the 194 patients excluded had SPT greater than 4 mm in diameter and were considered too high-risk for the study. Of the children randomized into groups for the study, 15.3% (98/640) had a positive SPT result on initial assessment. In the EAT study, 5.1% (33/652) of the early-introduction group had a positive SPT to one of the six foods being introduced. OFC were performed for these 33 infants and 7 infants had a positive challenge to at least one of the allergenic foods. The children in the EAT study were 3 months of age at the time these assessments were made suggesting that sensitization may be occurring even earlier than 3–4 months of age. Although a multitude of factors (i.e. gender, genetics, environmental factors) are likely to contribute to this, it questions the timing at which infants should be exposed to potential allergens. If early introduction is truly the best strategy as shown by the work already done, should future preventative strategies aim to expose children to food allergens earlier to prevent food allergy and if so,

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what methods would be safe and effective? Both in the LEAP and EAT studies, safety of early introduction was measured. The LEAP study reported no significant differences in serious adverse effects or rates of hospitalization between the peanut consumption and avoidance groups. Similarly, the EAT study concluded that early introduction was safe with no cases of anaphylaxis occurring during the initial introduction regimen as well as no effects on growth or breastfeeding of the infants. Choking related to a study food was not reported for both studies. However, the LEAP study design excluded 9.1% of the infants who were initially screened because they had SPT wheals >4 mm in diameter on baseline testing and were classified as high risk. They went on to have an OFC at 60 months of age and it was found that a SPT > 4 mm in this population of infants was predictive of peanut allergy at 60 months of age. It is in these children where potential future work is needed, as it is currently unknown whether early intervention in this group of children would be safe, effective and tolerated.

Conclusions

The evidence supporting the role of early introduction of potential allergens in the development of oral tolerance to prevent food allergy is mounting. Although there are still questions as to the timing and also which allergens can be introduced safely and with effect, a shift from recommending avoidance of common food allergens to early consumption strategies to prevent the development of food allergy is occurring. It appears that the window of opportunity for intervention is starting to close upon reaching the milestone of sitting and is almost entirely closed upon reaching the milestone of walking. Studies such as the LEAP study have already been influential in recommendations in order to prevent the development of peanut allergy. The EAT study results, in the per protocol population, support the LEAP findings and also demonstrate a reduction in egg allergy in the early introduction group. A clinical reduction in allergy could not be demonstrated for the other food allergens in EAT, but there were trends towards the reduction of both peanut and egg and the ingestion of these allergenic foods proved nutritionally safe. Indeed, there were many favourable nutritional outcomes related to early peanut introduction and ongoing consumption in the LEAP study. These recent advances towards food allergy prevention are extremely promising, but further work is required to establish if they will be as effective for other common food allergens.

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Conflict of interest

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